II. REMARKS/ARGUMENTS

A. Status of claims

Claims 38 and 47-52 are currently pending. Claims 1-37 and 39-46 were previously cancelled. No amendments have been made herein.

B. Information Disclosure Statement

Applicants submit herewith a copy of the January 25, 2002 PTO-Form 1449 (8 pages), as requested by the Examiner.

Applicants respectfully request that the references listed on the January 25, 2002 PTO-Form 1449 be considered and made of record.

C. Claim Rejections under 35 U.S.C. § 103(a)

1. Baker et al. in view of Furst

In the Office Action, claims 38, 47, 48, 51 and 52 were rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,569,937 to Baker et al. in view of Furst, D.E., "Meloxicam: Selective COX-2 inhibition in clinical practice", *Seminars in Arthritis and Rheumatism*, **26(1)**; pp. 21-27 (June 1997).

a. U.S. Patent 4,569,937 to Baker et al. in view of Furst does not render the claims obvious

This rejection is traversed. Applicants respectfully submit that the Baker reference in view of the Furst reference fails to teach or suggest "a method of effectively treating pain in humans comprising orally administering to a human patient an oral dosage form comprising two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) meloxicam and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof", as recited in the present claims.

b. The reference to NSAIDs in the Background of the Invention in the Baker reference specifically refers to the limited compounds in the Sunshine reference which do not include meloxicam

At the Examiner's own admission, "Baker et al. fail to disclose compositions with Meloxicam". The Examiner further stated that "Baker et al. only teach the use of NSAIDs like ibuprofen". Office Action at page 5. However, Applicants respectfully submit that the Baker reference does not teach or suggest the use of any NSAID, but solely teaches the use of a single specific NSAID, i.e., ibuprofen. Applicants note that there are only two instances to the general term "NSAID" in the Baker reference, at column 1, lines 17-27. These instances are to "selected NSAIDS" (emphasis added) of U.S. Patent No. 4,464,376 issued to A. Sunshine et al. (enclosed as Exhibit A in Applicants September 28, 2006 response). The Baker reference included the Sunshine reference in the background section indicating that the invention of Baker was *departing from* (and not *including*) the disclosure of the Sunshine reference, so for this reason alone the Baker reference teaches away from the disclosure of the Sunshine reference. In any event, the Sunshine reference teaches away from all but a select group of NSAIDs, the select group *not* including meloxicam.

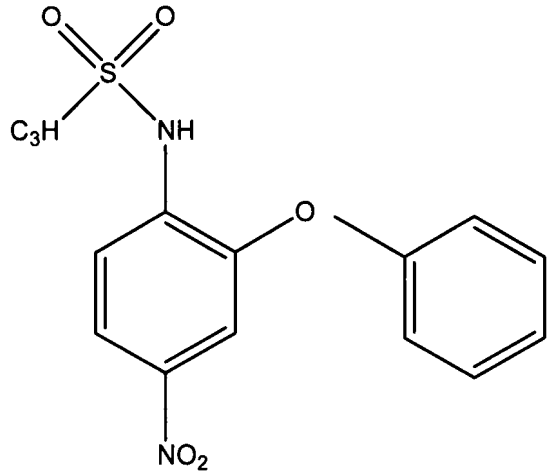
The Examiner's attention is directed to the Sunshine reference at column 14, lines 58-61, which recite "[t]he term 'selected NSAID' as used herein is intended to mean any non-narcotic analgesic/nonsteroidal anti-inflammatory compound **falling within one of the five structural categories indicated hereinabove**." (Emphasis added).

These five categories are set forth at column 7, lines 42-50 of the Sunshine reference which states that:

> The non-narcotic analgesics/nonsteroidal anti-inflammatory drugs for use in the compositions and methods of the present invention can be selected from the following categories:
> (1) the propionic acid derivatives;
> (2) the acetic acid derivatives;
> (3) the fenamic acid derivatives;

(4) the biphenylcarboxylic acid derivatives; and
(5) the oxicams.

The chemical structures of the (5) categories are exemplified in columns 8-11 of the Sunshine reference. Applicants submit that the chemical structure of the presently claimed NSAID, *i.e.* meloxicam:



does not fall within any of the five structural categories indicated above. Therefore, even assuming arguendo that the Baker reference contemplates the use of other NSAIDs based on the reference to the Sunshine reference, Applicants submit that the "other" NSAIDs would be limited to the five structural categories listed in the Sunshine reference and would not include meloxicam.

Furthermore, Applicants submit that the purported invention in the Sunshine reference is directed to combinations of caffeine and select NSAIDs; caffeine and narcotic analgesics; and caffeine and select NSAIDs/narcotic analgesics. Applicants respectfully submit that the present claims exclude the presence of caffeine by virtue of the "consisting of" terminology in the claims.

c. Furst does not compare the side effects of meloxicam and ibuprofen

In support of the rejection, the Examiner cited to Figure 2 of the Furst reference and stated that "Furst et al. shows that meloxicam is more potent than any other NSAID at reducing pain in clinical trials." (Office Action at page 7, emphasis added). Applicants respectfully point out that Figure 2 is not a comparison of meloxicam to any other NSAID, but rather is a comparison of meloxicam to four specific NSAIDs which include meloxicam, diclofenac, etodolac and nabumetone. In fact, Applicants submit that, in view of the teachings of the Furst reference, one of ordinary skill in the art would be motivated against replacing meloxicam for ibuprofen in the Baker reference, as none of the comparison studies for effectiveness of pain relief discussed in the Furst reference include ibuprofen. Thus, based on the discussion of the Furst reference, one of skill in the art would not be motivated to substitute meloxicam for ibuprofen, as the reference does not provide one of ordinary skill in the art any indication as to the efficaciousness of meloxicam versus ibuprofen. The Furst reference teaches away from such a substitution for ibuprofen.

d. There is conflicting evidence on the COX receptors and side effects associated with meloxicam and ibuprofen

Additionally, Applicants submit that it appears the Examiner is basing the present rejection on the assumption that meloxicam inhibits only COX-2 receptors, while ibuprofen inhibits only COX-1 receptors, and therefore meloxicam will not exhibit (or exhibit to a lesser extent) side effects usually associated with COX-1 receptor inhibition. Specifically, the Examiner stated that "[m]eloxicam exhibits less serious gastric and renal side effects than ibuprofen because it selectively inhibits COX-2 rather than COX-1" (Office Action at page 6). However, Applicants submit that there have been conflicting reports not only on the extent of side effects exhibited by meloxicam and ibuprofen, but also on the inhibition of the COX-2 and COX-1 receptors by meloxicam and ibuprofen. For example, Van Hecken et al. state that "diclofenac, ibuprofen, and naproxen...have been shown in vitro to be inhibitors of both COX-1

and COX-2" and further describes side effects of meloxicam that result from COX-1 activity. See Van Hecken et al., *J Clin Pharmacol* (2000); 40:1109-1120, 1116, enclosed herewith and listed as reference "AO" on the accompanying PTO Form 1449 (emphasis added). Even if there was agreement within the scientific community that meloxicam selectively inhibits COX-2, the reports of side effects of meloxicam have been conflicting and inconclusive. See, e.g., Richy et al. *Ann Rheum Dis* (2004); 63:759-766, 764, enclosed herewith and listed as reference "AP" on the accompanying PTO Form 1449, which provides a rank order of NSAIDs according to risk for GI complication, showing that meloxicam had a higher risk of GI complications than ibuprofen, and concluded that "ibuprofen was the safest drug". Id. at 764 (emphasis added). Additionally, Lanes et al. refer to previous studies in which "there is no convincing evidence that the risk of the severest adverse gastrointestinal events...is lower with meloxicam than with other NSAIDs". Lanes et al., *Pharmacoepidemiology and Drug Safety* (2000); 9:113-117, 113, enclosed herewith and listed as reference "AN" on the accompanying PTO Form 1449. In view of these references and the references cited by the Examiner, Applicants submit that it is improper to assume that meloxicam would necessarily exhibit less serious gastric and renal side effects than ibuprofen, as suggested by the Examiner, based on the references cited herein.

The reference discussed above are post-filing publications, however they are cited here to rebut the Examiner's presumption that "[m]eloxicam exhibits less serious gastric and renal side effects than ibuprofen because it selectively inhibits COX-2 rather than COX-1".

e. There is no motivation to substitute the ibuprofen in the synergistic combination of the Baker composition with any other NSAID

Applicants further submit that, in view of the above, the Baker reference teaches away from substituting ibuprofen with another NSAID (e.g., meloxicam), because of the unexpected synergy that it purports for the combination of ibuprofen with a narcotic analgesic. Accordingly, due to this purported synergy, one skilled in the art would be discouraged to combine the Baker reference with the Furst reference in order to select an NSAID different than ibuprofen (i.e.,

meloxicam) to combine with oxycodone. "A prior art reference may be considered to teach away when 'a person of ordinary skill, upon reading the reference would be discouraged from the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." See *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 45 USPQ2d 1977, 1984 (Fed. Cir. 1998). Therefore, Applicants submit that, as a whole, the Baker reference would steer one of ordinary skill in the art away from combining the Baker reference with the Furst reference to select an NSAID different than ibuprofen (i.e., meloxicam) to combine with oxycodone, for the reasons argued above.

In addition, Applicants submit that modifying the formulation of the Baker reference in view of the Furst reference, as proposed by the Examiner, by substituting meloxicam for ibuprofen would result in a dosage form which is not directed to the principle of operation described in the Baker reference (i.e., the purported synergism of narcotic analgesics and ibuprofen). "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious." See MPEP 8th edition, Revision 2, p.2100-132.

f. The Examiner is relying on an improper "obvious to try" rationale

Furthermore, Applicants submit that the Examiner is applying an improper "obvious to try" rationale in suggesting the substitution of ibuprofen with meloxicam. "In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir.1988). Applicants submit that *In re O'Farrell* is analogous to the present situation, where one of ordinary skill in the art would have to try each of numerous possible NSAIDs in place of ibuprofen in order to arrive at the selection of meloxicam, as the Baker reference in view of the

Furst reference provides no direction as to the selection of a particular NSAID to combine with oxycodone.

g. The Examiner is improperly picking and choosing meloxicam and oxycodone from the prior art

Applicants also submit that the Examiner is improperly picking and choosing the meloxicam of the Furst reference and the oxycodone of the Baker reference to recreate the claims of the present application. One "...cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention." *SmithKline Diagnostics, Inc. v. Helena Laboratories Corporation*, 859 F.2d 878, 887 (Fed. Cir. 1988).

Based on Applicants review of the Baker reference, it appears that the inventors in the Baker reference rejected all NSAIDs in their invention *except* ibuprofen. The purported invention and teachings of the Baker reference are limited to the combination of a narcotic analgesic and ibuprofen. For example, column 1, lines 6 - 9 of the Baker reference states as follows:

> *This invention relates to pharmaceutical compositions of narcotic analgesics and ibuprofen having analgesic activity in mammals, and to methods of use of the compositions to alleviate pain in mammals.*
> (Emphasis Added)

Column 2, lines 11-15 of the Baker reference states as follows:

> *According to the present invention there is provided a pharmaceutical composition comprising a combination of (a) a narcotic analgesic, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof,...*
> (Emphasis Added)

The following additional passages from the Baker reference are also limited to a combination of narcotic analgesics and ibuprofen:

Column/Lines	**Text**
Title:	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Abstract:	ABSTRACT Pharmaceutical compositions of narcotic analgesics and ibuprofen . . .
Figure 1	ISOBOLOGRAM FOR THE INTERACTION OF ORAL OXYCODONE HCL AND IBUPROFEN . . .
Col. 1, line 1 & 2	ANALGESIC MIXTURE OF OXYCODONE AND IBUPROFEN
Col. 2, lines 20-24	. . . synergistically effective analgesic amounts of oxycodone, or a pharmaceutically suitable salt thereof, and ibuprofen, or a pharmaceutically suitable salt thereof . . .
Col. 2, line 34 & 35	. . . various dose ratios of oxycodone and ibuprofen.
Col. 2, lines 64 & 65	In a composition of the invention, oxycodone and ibuprofen are combined . . .
Col. 3, lines 23 & 24	. . . unexpectedly enhanced analgesic activity of combinations of oxycodone and ibuprofen . . .
Col. 3, lines 53-56	. . . the active ingredient is administered at a daily dosage of from about 0.05 to 7.50 milligrams per kilogram (mg/kg) of body weight of oxycodone and from about 10 to 120 mg/kg of ibuprofen.
Col. 4, lines 24-29	Example 1 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 60.0
Col. 4, lines 36-42	Example 2 Oxycodone/Ibuprofen Tablets Oxycodone HCl 5.0 Ibuprofen 300.0
Col. 4, lines 48-55	Example 3 Oxycodone/Ibuprofen Tablets Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 4, lines 60-66	Example 4 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 60.0

Column/Lines	Text
Col. 5, lines 8-14	Example 5 Oxycodone/Ibuprofen Capsules Oxycodone HCl 5.0 Ibuprofen 300.00
Col. 5, lines 20-26	Example 6 Oxycodone/Ibuprofen Capsules Oxycodone HCl 2.5 Ibuprofen 300.0
Col. 5, lines 33-39	Example 7 Oxycodone/Ibuprofen Tablets Oxymorphone HCl 5.0 Ibuprofen 60.0
Col. 5, lines 45-51	Example 8 Oxymorphone/Ibuprofen Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 5, lines 58-63	Example 9 Oxymorphone/Ibuprofen Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 1-7	Example 10 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 60.0
Col. 6, lines 13-19	Example 11 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 5.0 Ibuprofen 300.0
Col. 6, lines 25-31	Example 12 Oxymorphone/Ibuprofen Capsules Oxymorphone HCl 2.5 Ibuprofen 300.0
Col. 6, lines 38-43	Example 13 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 6, lines 49-55	Example 14 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 5.0 Ibuprofen 300.0

Column/Lines	Text
Col. 6, lines 61-66	Example 15 Hydrocodone/Ibuprofen Tablets Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 9-14	Example 16 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 60.0
Col. 7, lines 21-27	Example 17 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 5.0 Ibuprofen 300.0
Col. 7, lines 33-39	Example 18 Hydrocodone/Ibuprofen Capsules Hydrocodone Bitartrate 2.5 Ibuprofen 300.0
Col. 7, lines 46-51	Example 19 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 7, lines 57-63	Example 20 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 3.0 Ibuprofen 300.0
Col. 8, lines 1-7	Example 21 Hydromorphone/Ibuprofen Tablets Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 13-19	Example 22 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 60.0
Col. 8, lines 26-31	Example 23 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 3.0 Ibuprofen 300.0
Col. 8, lines 37-43	Example 24 Hydromorphone/Ibuprofen Capsules Hydromorphone HCl 1.5 Ibuprofen 300.0
Col. 8, lines 56-58	All mice are dosed sequentially by the oral route with suspensions of ibuprofen and/or oxycodone hydrochloride solutions.

Column/Lines	Text
Col. 8, line 62	A stock suspension of ibuprofen is . . .
Col. 9, lines 22-24	Mice, intubated with various doses of oxycodone hydrochloride, ibuprofen, combined doses of oxycodone hydrochloride and ibuprofen . . .
Col. 9, lines 45-47	In order to study the interaction between oxycodone and ibuprofen, 5 precise dosage ratios of oxycodone hydrochloride and ibuprofen are selected.
Col. 10, lines 25 & 26	The synergistic interaction of oxycodone hydrochloride and ibuprofen . . .
Col. 10, lines 29-31	. . . the analgesic effect of oxycodone along is presented in the ordinate, and that of ibuprofen alone is on the abscissa.
Col. 10, lines 32-34	. . . exact fixed dosage ratios based on weight of oxycodone HCl:ibuprofen in the ranges of 1:1.25 to 1:31.1.
Col. 10, lines 35 & 36	. . . representing oxycodone and ibuprofen alone . . .
Col. 10, lines 36-38	. . . representing the compositions of oxycodone and ibuprofen at the fixed dosage ratios.
Col. 11, lines 31-33	. . . straight line additivity hypothesis for oxycodone HCl and ibuprofen . . .
Col. 12, lines 52-54	. . . analgesic synergism is established for all combinations of oxycodone and ibuprofen.
Col. 12, lines 55 & 56	By substitution of the expected analgesic activity of oxycodone alone and ibuprofen alone . . .
Col. 12, lines 62 & 63	. . . it is predicted that oxycodone and ibuprofen would demonstrate analgesic potentiation . . .
Table 1	TABLE 1 ORAL OXYCODONE HCl/IBUPROFEN COMBINATIONS Oxycodone Ibuprofen Oxycodone Ibuprofen
Col. 13, lines 49-55	1. A pharmaceutical composition comprising a synergistic analgesic combination of (a) oxycodone, or a pharmaceutically acceptable salt thereof, and (b) ibuprofen, or a pharmaceutically suitable salt thereof, in which the weight ratio of (a):(b) is from about 1:6 to about 1:400.

As evidenced above, ibuprofen is the only NSAID mentioned throughout the entire reference, and it is the only NSAID exemplified in the Baker formulations.

In view of the above, Applicants respectfully submit that the 35 U.S.C. 103(a) rejection over the Baker reference in view of the Furst reference be removed.

2. Baker et al. in view of Furst, Oshlack I et al., Oshlack II et al. and Iyengar et al.

In the Office Action, the Examiner further rejected claim 49 under U.S.C. 103 (a) over Baker et al. in view of in view of Furst, U.S. Patent No. 5,472,712 to Oshlack et al. (Oshlack I), U.S. Patent No. 6,294,195 to Oshlack et al. (Oshlack II) and PCT Publication No. WO 97/25988 to Iyengar et al.

As discussed above, Applicants respectfully submit that the Baker reference in view of the Furst reference fails to teach or suggest "a method of effectively treating pain in humans comprising orally administering to a human patient an oral dosage form comprising two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) meloxicam and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof", as recited in the present claims.

With respect to Oshlack I, Oshlack II and Iyengar, Applicants respectfully submit that these references fail to cure the deficiencies of the combination of the Baker reference and the Furst reference. In support of this position, Applicants submit that Oshlack I, Oshlack II and Iyengar fail to motivate one skilled in the art to modify the combination of the Baker reference and the Furst reference to arrive at "a method of effectively treating pain in humans comprising orally administering to a human patient an oral dosage form comprising two analgesic compounds and/or pharmaceutically acceptable salts thereof consisting of (i) meloxicam and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof", as recited in the present claims.

Accordingly, Applicants respectfully request that the 35 U.S.C. 103(a) rejection over the Baker reference in view of the Furst, Oshlack I, Oshlack II and Iyengar references be removed.

III. CONCLUSION

In view of the foregoing, it is believed that the application is now in condition for allowance, and applicants respectfully request such action.

The Examiner is respectfully requested to contact the undersigned at the telephone number provided below in the event that a telephonic interview will advance the prosecution of the application.

Respectfully submitted,
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